REMARKS

These remarks are in response to the Office Action mailed August 21, 2003. Claims 4-5 and 7-8 have been canceled without prejudice to Applicants' right to prosecute the canceled subject matter in any divisional, continuation, continuation-in-part, or other application. Applicants have amended claims 1, 9 and 10. Support for the amendment to claims 1 and 9 can be found throughout the specification and claims as originally filed. New claims 23-26 have been added. Support for the new claims can be found, for example, in original claims 10-15 and throughout the specification. No new matter is believed to have been introduced.

I. REJECTION UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claims 9 and 10 stand rejected under 35 U.S.C. §112, first paragraph, because the specification while being enabling for a pharmaceutical composition comprising the vector of claim 1, wherein the composition is directly administered to a tumor in an animal, allegedly does not reasonably provide enablement for any method of delivery. Applicants respectfully traverse this rejection.

The Examiner is respectfully directed to page 17, lines 7-9, which indicates that the vector can be administered intravenously. Furthermore, the specification teaches that such intravenous administration demonstrates efficacy. Thus, the specification teaches, as admitted in the Office Action, that (i) the vector can be directly administered to a tumor, and (ii) the vector can also be administered intravenously. Accordingly, the claims are of a scope that is fully enabled by the specification and the §112, first paragraph rejection may be properly withdrawn.

II. REJECTION UNDER 35 U.S.C. §102

Claims 1-5 and 7-10 stand rejected under 35 U.S.C. §102 as allegedly anticipated by Hall et al. (WO98/44938; hereinafter "Hall et al."). Claims 4-5 and 7-8 have been canceled, thus the rejection is moot with respect to these claims. Applicants respectfully traverse this rejection.

Applicants respectfully submit that the disclosure provided by Hall et al. is not enabling for treating cancers using a retroviral particle comprising a modified viral surface protein comprising a von Willebrand collagen binding domain and a polynucleotide encoding GM-CSF. For example, the Examiner is directed to pages 21-22 of Hall et al. which describes methods of treating tumors. In the description there is no reference of GM-CSF expression to treat such tumors. Applicants demonstrate herein that expression of GM-CSF at tumor locations resulted in reduced tumor mass. In addition, Applicants demonstrate the unexpected result of GM-CSF expression including recruitment of host mononuclear cells to the cite of the tumor thereby promoting tumor degradation. Such unexpected results are not taught or suggested by Hall et al. Furthermore, Hall et al. do not teach or suggest how to design or express Applicants' claimed vector. Rather, Hall et al. teach and suggest only that a retroviral vector having a modified surface protein for targeting the vector to extracellular matrix can also comprise a heterogeneous polynucleotide (i.e., a therapeutic agent).

As the Examiner indicated in the Office Action at page 3, the field of gene transfer in vivo continues to be unpredictable and inefficient. The Hall et al. reference fails to demonstrate the treatment of tumors in vivo. In contrast, Applicants demonstrate in vivo results and unexpected properties including mononuclear cell recruitment. Accordingly, Hall et al. is not

enabled for what the Examiner purports in the Office Action. Thus, the rejection should be withdrawn.

III. REJECTION UNDER 35 U.S.C. §103

Claims 1-5 and 7-10 stand rejected under 35 U.S.C. §103 as allegedly unpatentable over Hall et al. (WO 98/44938; hereinafter "Hall-1") or Hall et al. (Human Gene Therapy 11:983-993, 2000; hereinafter "Hall-2") or Liu et al. (J. Virol. 74:5320-5328, 2000) or Gordon et al. (Cancer Research 60:3343-3347, 2000) in view of Kurane et al. (Ann. Of Surgery 4:579-585, 1997) and Borrello et al. (Human Gene Therapy 10:1983-1991, 1999). Claims 4-5 and 7-8 have been canceled, thus the rejection is moot with respect to these claims. Applicants respectfully traverse this rejection.

Applicants respectfully submit that the Patent Office has set forth a double standard. On one hand the Patent Office alleges that gene therapy and gene delivery are highly unpredictable arts and thus applicants should not be entitled to claim genetic delivery methods or gene therapy absent data in specific models under specific conditions. The Patent Office then alleges that it would be a simple matter to arrive at applicants' gene therapy or gene delivery by merely combining the teachings in the art. Such is the case presented here.

The Patent Office indicates in the §112 rejection above,

> The specification as filed is not enabling for the invention commensurate with the full scope of the claims because the art of targeting a therapeutic gene to any tissue using any retroviral vector is unpredictable as has been recognized by [sic] one of skill in the art and therefore *would require undue experimentation*.

(See, page 2, last paragraph of the Office Action; emphasis added). The Office Action then alleges at page 6,

> At the time of the invention, it would have been obvious to an artisan of skill to modify the vector(s) of Hall et al. Liu et al. or Gordon et al. by cloning the GM-CSF encoding sequence taught by Borrello et al. with *a reasonable expectation of success* and use the resultant vector for delivering GM-CSF to a tumor in an animal.

(Emphasis added). Thus, on the one hand undue experimentation is required to enable gene delivery and gene therapy related to Applicants' invention but at the same time it would have a reasonable expectation of success.

Applicants address Hall-1 above and submit that Hall-1 is not enabled for what the Examiner purports Hall-1 teaches and/or suggests. Applicants submit that Hall-1 does not teach or suggest how to make and/or use a retroviral particle comprising a surface protein that binds to extracellular matrix material and a cytokine gene (e.g., GM-CSF) as recited in claim 1.

The Examiner admits that Hall-2, Liu et al. and Gordon et al. do not teach a targeted vector comprising a cytokine or GM-CSF (see page 6). In order to overcome that deficiencies of Hall-2, Liu et al. and Gordon et al., the Examiner combines Kurane et al., and Borrello et al. for the teaching that cytokines can be used as adjuvants. However, in keeping with the Patent Office's position on gene therapy and gene delivery, Applicants submit that it would require undue experimentation and that gene delivery/therapy is highly unpredictable. Thus, there would be no reasonable expectation of success in combining the teachings of the references.

Obviousness requires a reasonable expectation of success. *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986); MPEP §2143.02. Whether an art is predictable or whether the proposed modification or combination of the prior art has a reasonable expectation of success is determined at the time the invention was made. *Ex parte Erlich*, 3 USPQ2d 1011 (Bd. Pat.

App. & Int'f. 1986); MPEP §2143.02. In light of the teachings of the reference and the position of the Patent Office, Applicants submit that one of ordinary skill in the art would not have any reasonable expectation of success in combining mere cytokine therapy with gene delivery. Nothing in the art cited by the Examiner indicates success of Applicants' claimed invention or a probability of success, thus it would not have been reasonable to expect the success of the instant invention until it was reduced to practice. Applicants submit that there is no enabling disclosure that provides methods to construct a vector as claimed by Applicants. Furthermore, there is no enabling disclosure that provides evidence that such gene delivery using a vector of the invention can be used to treat tumors. Thus, Applicants have provided a showing there was no reasonable expectation of success thus supporting the position that the claimed invention is nonobviousness. *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA1976); MPEP §2143.02. *See also Amgen, Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir.), *cert. denied*, 502 U.S. 856 (1991).

For at least the foregoing reasons, Applicants respectfully request withdrawal of the §103 rejection over the cited references.

Applicant asks that all claims be allowed. Enclosed is a $475 check for the Petition for Extension of Time fee. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: 2/13/04

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